Single Agent Oral Selinexor in Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL): Phase 2b SADAL Study

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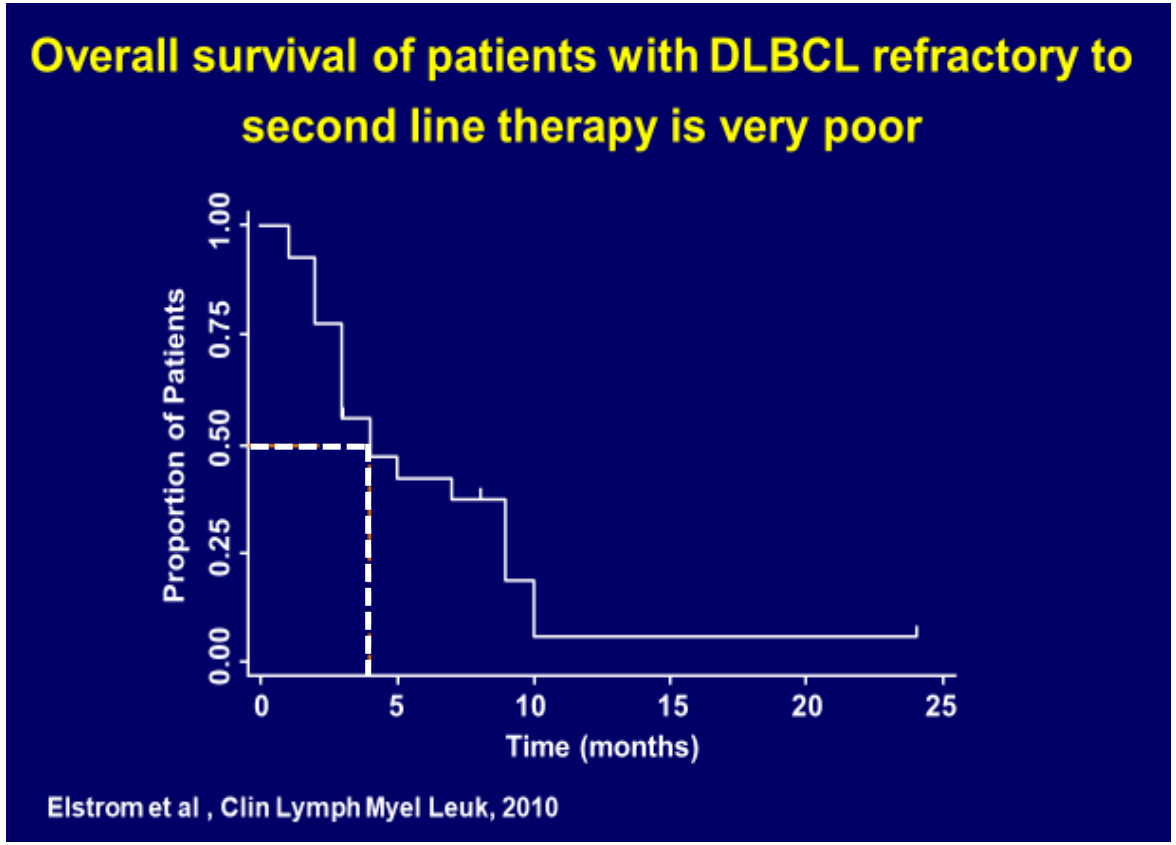
Selinexor is an investigational therapy not approved by EMA or FDA

Background – Relapsed DLBCL

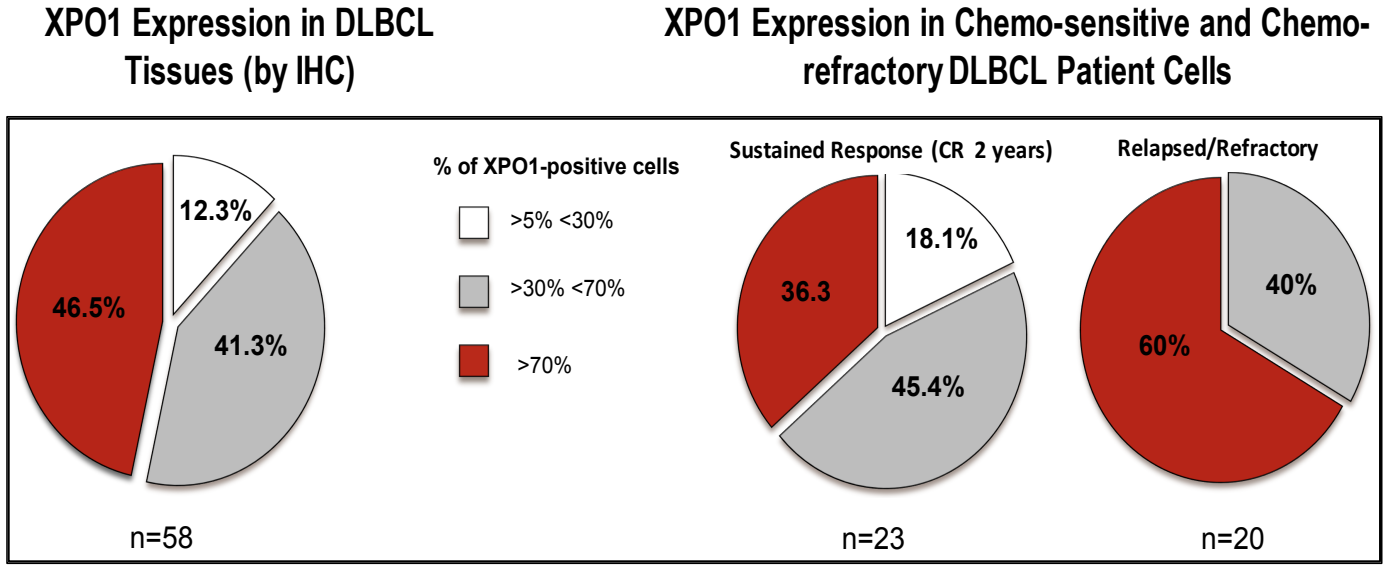


- Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma
- ~60% of patients are cured with frontline combination chemotherapy + anti-CD20 antibodies
- Relapsed or refractory DLBCL can be cured by platinum-based chemoregimens followed by high dose chemotherapy and stem cell transplantation (Gisselbrecht, CORAL study, JCO 2010)

- The patients that have failed second line therapy or are not candidates for transplantation have a very poor outcome (Crump, SCHOLAR study, ASCO 2016)
  - Overall Response Rate: ~25% with available agents
  - Median Overall Survival: < 6 months
- R/R DLBCL represents a significant unmet medical need

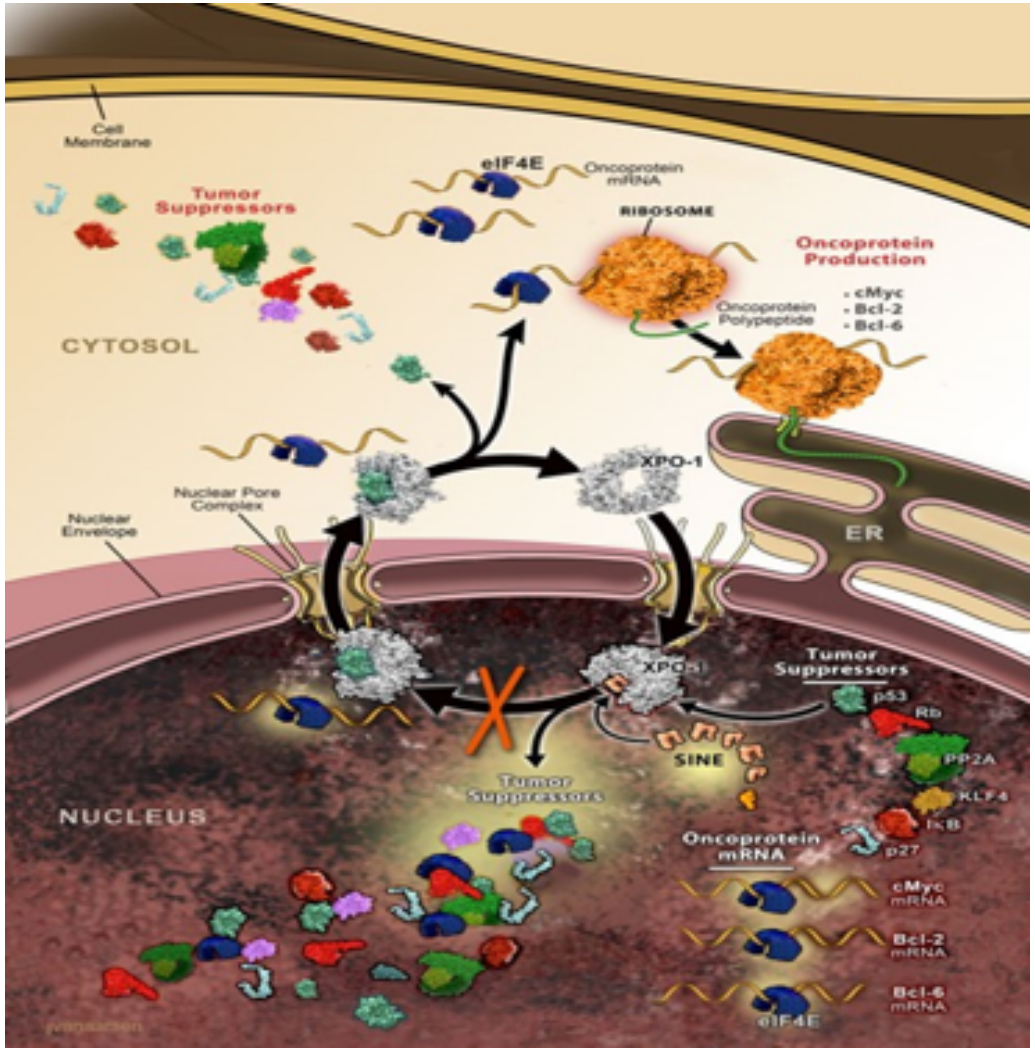
Background – Exportin 1 (XPO1)

- XPO1 is the major nuclear export protein for which transports certain proteins from the nucleus to the cytoplasm including:
  - Tumor Suppressor Proteins (TSPs)
  - Oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, MDM2 and cyclins)
- XPO1 in cancer cells:
  - Inactivates TSPs by nuclear exclusion
  - Contributes to cell proliferation
- XPO1 is overexpressed in DLBCL; 60% of R/R DLBCL having >70% XPO1 positive cells



Marullo AACR 2015

Selinexor – Mechanism of Action



- Selinexor:
  - Oral small molecule, first-in-class inhibitor of XPO1, inhibits cell growth and tumor apoptosis
  - Reactivates multiple TSPs and reduces oncoproteins known to play critical roles in NHL
  - Blocks NF-κB activation

- Phase I study of selinexor, monotherapy demonstrated activity in heavily pretreated lymphomas including GC/nonGC subtypes and DH DLBCL (*Kuruvilla, Blood 2017*). Responses were durable

SADAL Study Design – NCT 02227251

- A randomized Phase 2B study comparing 60 mg *vs.* 100 mg single agent oral selinexor in patients with relapsed/refractory diffuse large B-Cell lymphoma (DLBCL)
  - Stratified by cell-of-origin subtype (GCB or non-GCB)
  - Twice Weekly / 28 Day Cycle

- **Endpoints:**
  - Primary: Overall Response Rate (ORR), according Lugano Criteria 2014 *(Cheson, JCO, 2014)*
  - Secondary: Duration of Response (DOR), OS, and safety

- **Main Inclusion/Exclusion Criteria:**
  - Patients ≥18 years with clinical or radiographic evidence of progressive DLBCL
  - Received at least 2 to maximum 5 previous systemic therapies (including anthracycline and mabthera)
  - ≥14 weeks from last treatment
  - Excluded, any significant organ failure or ANC <1,000/mm^3 or platelets <75,000/mm^3,

Baseline Patient Characteristics

	60 mg	100 mg
Patients Enrolled as of May 15, 2017 (N=90)	**46**	**44**
Median Age, Years (range)	68 (44 – 87)	66 (30 – 83)
Males : Females	29 M : 17 F	28 M : 16 F
de novo DLBCL : Transformed DLBCL	74% de novo : 26% trans	70% de novo : 30% trans
GCB Subtype	22 (48%)	23 (52%)
Non-GCB Subtype	24 (52%)	21 (48%)
Median Prior Regimens (range)	**3 (2 – 5)**	**3 (2 – 5)**
- Prior Stem Cell Transplant	13 (28%)	18 (41%)
R-IPI Risk (*Sehn 2007*)		
- High Risk	7 (15%)	7 (16%)
- High Intermediate Risk	18 (39%)	15 (34%)
- Low Intermediate Risk	14 (31%)	15 (34%)
- Low Risk	6 (13%)	5 (11%)
- Unknown	1 (2%)	2 (5%)

Safety – Related Adverse Events Occurring in ≥10% of Patients (N=90)

AE Term	60 mg N=46				100 mg N=44			
Gastrointestinal	**Grade 1/2**	**Grade 3**	**Grade 4**	**G 3/4 Total**	**Grade 1/2**	**Grade 3**	**Grade 4**	**G 3/4 Total**
Nausea	21 (45.7%)	3 (6.5%)	--	**3 (6.5%)**	19 (43.2%)	3 (6.8%)	--	**3 (6.8%)**
Anorexia	18 (39.1%)	1 (2.2%)	--	**1 (2.2%)**	19 (43.2%)	6 (13.6%)	--	**6 (13.6%)**
Vomiting	16 (34.8%)	--	--	**--**	11 (25%)	1 (2.3%)	--	**1 (2.3%)**
Diarrhea	14 (30.4%)	1 (2.2%)	--	**1 (2.2%)**	13 (29.5%)	3 (6.8%)	--	**3 (6.8%)**
Altered Taste	6 (13%)	--	--	**--**	2 (4.5%)	--	--	**--**
Constipation	6 (13%)	--	--	**--**	4 (9.1%)	--	--	**--**
Constitutional								
Fatigue/Asthenia	22 (47.8%)	5 (10.9%)	--	**5 (10.9%)**	17 (38.6%)	11 (25%)	--	**11 (25%)**
Weight Loss	12 (26.1%)	--	--	**--**	17 (38.6%)	1 (2.3%)	--	**1 (2.3%)**
Hematologic								
Thrombocytopenia	6 (13%)	8 (17.4%)	5 (10.9%)	**13 (28.2%)**	8 (18.2%)	9 (20.5%)	9 (20.5%)	**18 (41%)**
Anemia	8 (17.4%)	7 (15.2%)	--	**7 (15.2%)**	8 (18.2%)	4 (9.1%)	--	**4 (9.1%)**
Neutropenia	4 (8.7%)	5 (10.9%)	3 (6.5%)	**8 (17.4%)**	2 (4.5%)	6 (13.6%)	2 (4.5%)	**8 (18.2%)**
Other								
Hyponatremia	1 (2.2%)	3 (6.5%)	--	**3 (6.5%)**	1 (2.3%)	4 (9.1%)	--	**4 (9.1%)**
Dizziness	2 (4.3%)	--	--	**--**	7 (15.9%)	--	--	**--**

Causes of Treatment Discontinuation (N=69)

	60 mg (N=44)	100 mg (N=46)
Patients Off Treatment	34 (74%)	35 (80%)
Progressive Disease	21 (62%)	17 (49%)
Toxicity	**6 (18%)**	**11 (31%)**
Death	4 (12%)	3 (9%)
Other	3 (9%)	4 (11%)
Median Dose Received	51 mg	71 mg

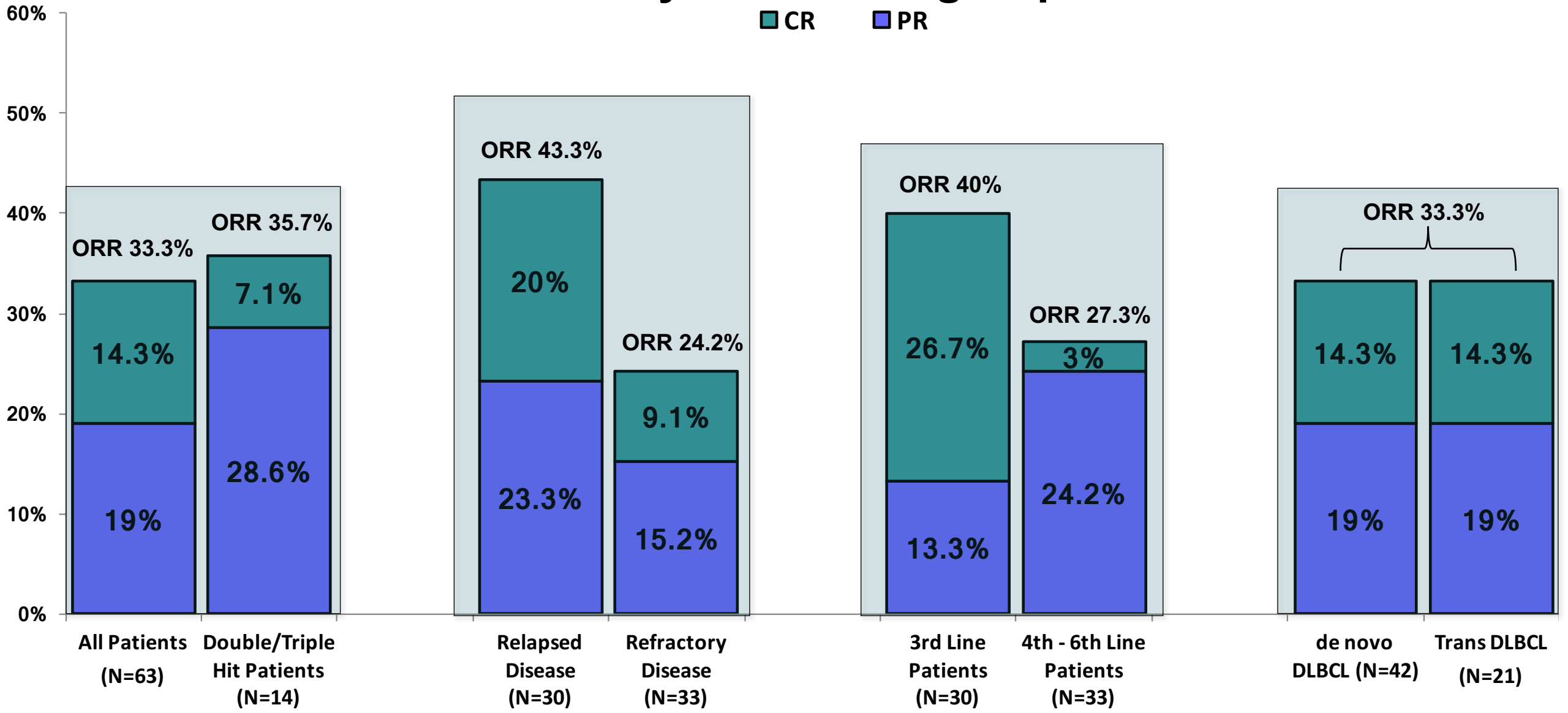
Efficacy – Pre-Specified Interim Analysis First 63 Patients

Best Responses† in the First 63 Patients as of May 15, 2017					
Category	**All Patients (N=63)**	**60 mg (N=32)**	**100 mg (N=31)**	**GCB (N=32)**	**Non-GCB (N=31)**
ORR (%)	**21 (33.3%)**	**11 (34.4%)**	**10 (32.2%)**	**9 (28.1%)**	**12 (38.7%)**
CR (%)	9 (14.3%)	4 (12.5%)	5 (16.1%)	4 (12.5%)	5 (16.1%)
PR (%)	12 (19.0%)	7 (21.9%)	5 (16.1%)	5 (15.6%)	7 (22.6%)
SD (%)	6 (9.5%)	1 (3.1%)	5 (16.1%)	3 (9.4%)	3 (9.7%)
PD/NE (%)	36 (57.1%)	20 (62.5%)	16 (51.6%)	20 (62.5%)	16 (51.6%)

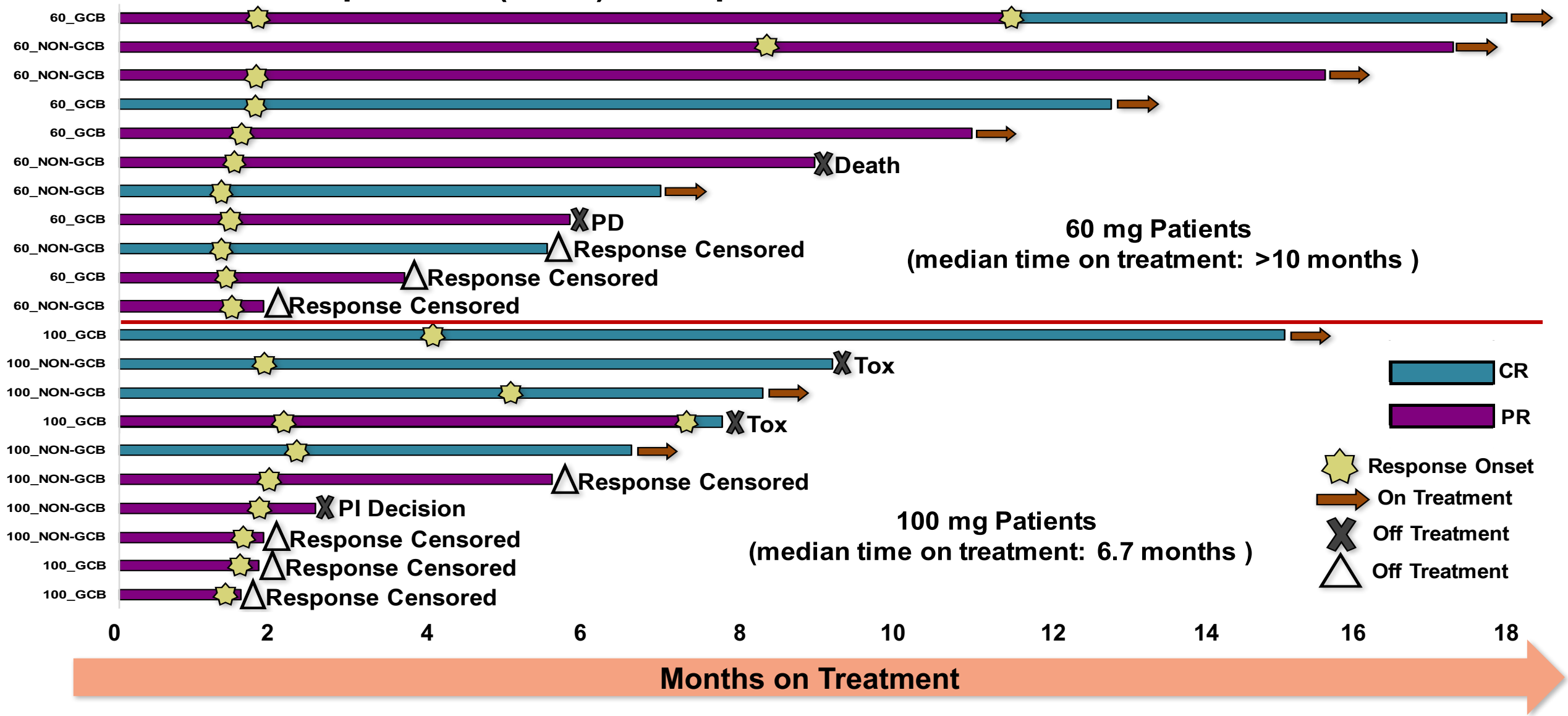
†Responses were adjudicated according to the Lugano Classification *(Cheson, 2014)* by an independent central radiological review committee. ORR=Overall Response Rate (CR+PR), CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Non-evaluable. Responses are based on interim unaudited data as of May 15, 2017 for the first 63 patients (of 90 total patients).

Overall response rate as determined by an independent central radiological review

Efficacy – ORR Subgroups

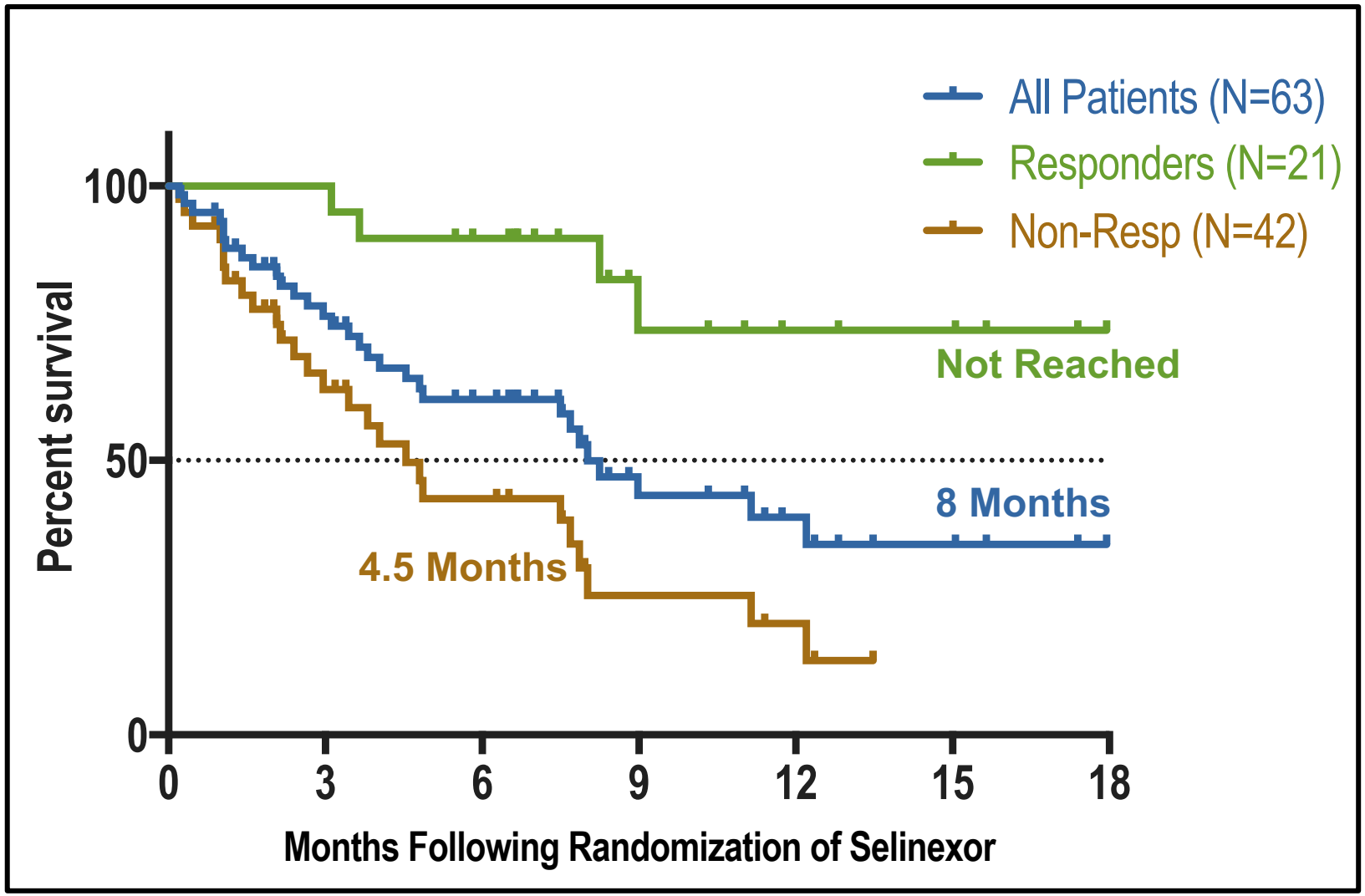


Responders (N=21) – Response Onset & Time on Treatment



Among 21 responders, the median time on treatment was 9 months (median DOR >7 months, with a FUP of 13 months) 9 responders remain on treatment including 6 patients in CR

SADAL Efficacy – Overall Survival



Summary and Conclusions

- Selinexor, a first in class XPO1 inhibitor, has demonstrated activity in R/R DLBCL

- **Overall Response Rate of 33.3%**
  - Response rates were similar across subgroups (60 mg, 100 mg, GCB, non-GCB, DH/TH patients)
  - Median of DOR >7 months including prolonged CRs
  - The median overall survival is 8 months (median not reached in responding patients)

- Most common adverse events:
  - Fatigue, nausea, anorexia, vomiting (mainly grade 1/2), and thrombocytopenia (mainly grade 3/4)
  - AEs can be managed with supportive care, dose reductions / interruptions
  - 60 mg was better tolerated than 100 mg with less dose reductions or discontinuations

- Based on AE profiles, discontinuation rates, efficacy signals:
  - The 100 mg arm was discontinued
  - Enrollment is ongoing with an additional 90 patients to be enrolled on the 60 mg arm

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